# A randomized, double-blind, double dummy, placebo-controlled, four-way, cross-over, single dose study to investigate the effects of paracetamol and THC on the PainCart in healthy subjects using promethazine as negative control

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To investigate the analgesic profile of different classical and non-classical analgesic compounds using a battery of pain tests (PainCart) in healthy subjects compared to a negative control.Secondary:- Investigate the association between subjective...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON42337

**Source**
ToetsingOnline

**Brief title**
PainCart validation: Paracetamol, THC and promethazine

### Condition

- Other condition

**Synonym**
Algesia, pain

**Health condition**

Pain

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Centre for Human Drug Research
**Source(s) of monetary or material Support:** CHDR Foundation

## Intervention

**Keyword:** Cannabinoids, Negative control, PainCart, Validation

## Outcome measures

**Primary outcome**

Pharmacodynamic endpoints

- Thermal Pain (Normal Skin): Pain Detection Threshold (PDT).

-Thermal Pain (UVB Skin): Pain Detection Threshold (PDT).

- Electrical Stair (pre-cold pressor): Pain Tolerance Threshold (PTT).

- Pressure Pain: Pain Tolerance Threshold (PTT).

- Cold Pressor: Pain Tolerance Threshold (PTT).

- VAS Feeling high

**Secondary outcome**

Pharmacodynamic endpoints

- Electrical Stair (pre-cold pressor): Pain Detection Threshold (PDT), Area

Under the Visual Analogue Scale (VAS) pain Curve (AUC), and post-test VAS.

- Electrical Stair (post-cold pressor): PDT, PTT, AUC, and post-test VAS.

- Conditioned Pain Modulation Response (change from electrical stair pre- and

post cold pressor): PDT, PTT, AUC.

- Evoked potentials: somatosensory evoked potentials (SEP) using the electrical stimulus measuring peak-to-peak (PtP) somatosensory evoked potentials (SEP) amplitude in vertex EEG, or other exploratory endpoints.

- Pressure Pain: PDT, AUC, and post-test VAS.

- Cold Pressor: PDT, AUC, and post-test VAS.

- VAS Bond & Lader (Alertness, mood, calmness)

- VAS Bowdle (internal perception, external perception, *feeling high*)

- Pharmaco-EEG: power (resting eyes closed, open and during pressure pain and cold pressor).

- Adverse events, laboratory safety, blood pressure, pulse rate and ECG parameters

Pharmacokinetic analysis will only be performed if relevant pharmacodynamic effect is observed.

The following endpoints will be determined for Δ9-THC and its active metabolites 11-OH-THC and THC-COOH; promethazine and paracetamol. They will be derived by non-compartmental analysis of the plasma concentration-time data:

- The area under the plasma concentration-time curve from zero to infinity(AUC0-inf);

- The maximum plasma concentration (Cmax);

- The area under the plasma concentration-time curve from zero to t of the last measured concentration above the limit of quantification (AUC0-last);

- The time to reach maximum plasma concentration (tmax);

- The terminal disposition rate constant (*z) with the respective half-life

(t*).

- Other parameters, including Vz/F, CL/F, and other parameters as appropriate,

as well as dose adjusted parameters, may be determined.

# Study description

### Background summary

The complex clinical reality of pain medicine demands novel analgesic therapeutics. Different cannabinoids have been shown to be effective in various pain conditions, including neuropathic pain related to multiple sclerosis or and pain related to oncological disease. The PainCart could be a useful tool to investigate the analgesic properties of novel active pharmaceutical ingredients including cannabinoid formulations, but needs to be pharmacologically validated for this specific class of compounds. In addition, potential sedative effects rather than analgesic effects of psychoactive compounds need to be investigated as part of the pharmacological validation of the PainCart.

The current study aims to investigate the analgesic effects of a compound targeting the cannabinoid system: Δ9-THC (Namisol®, ECP002A, oral formulation developed by Echo Pharmaceuticals), and, the still not completely understood mechanism of action most widely used analgesic, paracetamol (acetaminophen, generic oral formulation) using a validated pain test battery. In addition, promethazine will be included to investigate the effects of sedation on the PainCart outcome measures.

### Study objective

To investigate the analgesic profile of different classical and non-classical analgesic compounds using a battery of pain tests (PainCart) in healthy subjects compared to a negative control.

Secondary:
- Investigate the association between subjective psychotropic effects (*Feeling high* and changes in internal and/or external perception) and cannabinoid analgesia.
- Investigate the association between subjective sedative effects (Changes in alertness, mood and calmness) and cannabinoid analgesia.

- Investigate the feasibility, applicability, safety, tolerability, and reproducibility of the pain test battery in healthy subjects.
- Investigate the similarity between the analgesic profile of paracetamol and Δ9-THC using the PainCart test battery.
- Investigate the similarity between the subjective sedative effects (changes in alertness, mood and calmness) of Δ9-THC and promethazine.

**Study design**

This will be a randomized double-blind, double dummy, placebo-controlled, four way cross-over single dose study.

**Intervention**

During the course of the study, on every one of the study days, a subject will get, in random order:
- Δ9-Tetrahydrocannabinol (Δ9-THC, Namisol®, ECP002A/5), provided by Echo Pharmaceuticals, \ (2 tablets of 5 mg will be administered) and matching placebo (ECP002A/5P, oral tablets)
- Paracetamol (1 g) and matching placebo, oral capsule
- Promethazine (50 mg) and matching placebo, oral capsules

**Study burden and risks**

The current formulation of Δ9-THC (Namisol ®) has been administered in multiple studies including healthy volunteers and different patient populations. Δ9-THC has potential side effects, but is generally considered safe, even in high dosages. Possible side effects include confusion, hallucinations, delusions, decreased coordination, dizziness, drowsiness, elevated or relaxed mood, anxiety, headache, nausea, stomach pain, trouble concentrating, vomiting and weakness. No specific antidotes are deemed necessary.

Paracetamol is a mild analgesic and antipyretic, and is recommended for the treatment of most painful and febrile conditions, for example, headache including migraine and tension headaches, toothache, neuralgia, backache, rheumatic and muscle pains, dysmenorrhoea, sore throat, and for relieving the fever, aches and pains of colds and flu. Also recommended for the symptomatic relief of pain due to non-serious arthritis. Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia, neutropenia, pancytopenia, leukopenia and agranulocytosis but these were not necessarily causality related to paracetamol.

Promethazine is a classic H1-antihistamine with some anticholinergic effects. Daily doses up to 150 mg are prescribed for the treatment of allergic rhinitis and motion sickness. Singles doses up to 50 mg are prescribed to induce mild

sedation. Adverse effects are mostly observed in the realm of CNS depression. In addition, its anticholinergic effects increase the risk of narrow-angle glaucoma or prostatic hyperthrophy. Both of which are not relevant for the population under investigation. Finally, drug-induced phototoxicity has been reported for promethazine. However, UV-A radiation is considered to be the driving force behind this, rather than the UV-B radiation used in the UVB model.(13) In addition, the timing of UVB exposure 24 hours prior to a single drug administration, minimise the risk for the subjects of developing a phototoxic reaction.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Healthy subjects, 18 to 45 years of age, inclusive. Healthy status is defined by absence of

evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis;
2. Female subjects are required to have an intrauterine device, a contraceptive implant or are willing to continuously use oral contraceptives (i.e. skip their menstruation) during the study period;
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg and a maximum weight of 100 kg;
4. Able to participate and willing to give written informed consent and to comply with the study restrictions.

## Exclusion criteria

1. Legal incapacity or inability to understand or comply with the requirements of the study;
2. Clinically significant findings as determined by medical and psychiatric history taking, physical examination, ECG and vital signs;
3. Haemodynamic status at screening: systolic <100 and >160 mmHg, diastolic <50 and >95 mmHg, heart rate <45 and >100 bpm measured on the non-dominant (non-leading/non-writing hand) arm;
4. Any current, clinically significant, known medical condition in particular any existing conditions that would affect sensitivity to cold (such as atherosclerosis, Raynaud*s disease, urticaria, hypothyroidism) or pain (disease that causes pain, hypesthesia, hyperalgesia, allodynia, paraesthesia, neuropathy, etc.);
5. Subjects indicating pain tests intolerable at screening or achieving tolerance at >80% of maximum input intensity for any pain test for cold, pressure and electrical tests;
6. Have a urine drug screen detecting illicit drug of abuse (morphine, benzodiazepines, cocaine, amphetamine, THC, methamphetamines, MDMA) or a positive alcohol breath test at screening;
7. Consume, on average, >8 units/day of (methyl)xanthines (e.g. coffee, tea, cola, chocolate) and not able to refrain from use during each stay at the CHDR clinic;
8. History or clinical evidence of alcoholism or drug abuse;
9. Smoking of >5 cigarettes/day or equivalent and not able to abstain from smoking cigarettes during each stay at the CHDR clinic;
10. Use of prescription medication, over-the-counter medication, or herbal supplement within 7 days of nociceptive assessments;
11. Participation in a clinical trial within 90 days of screening or more than 4 times in the previous year;
12. Loss of blood >= 500 mL within 3 months (males) or 4 months (females) before screening;
13. Known hypersensitivity to the investigational drug or comparative drug or drugs of the same class, or any of their excipients;
14. Dark skin (Fitzpatrick skin type V or VI), wide-spread acne, tattoos or scarring on back; and/or
15. Subjects of childbearing potential who are unwilling or unable to use a highly effective barrier method of contraception for the duration of the study and for 3 months after the last

dose of study treatment.

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 07-09-2015 |
| Enrollment: | 24 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Namisol |
| Generic name: | Δ9-Tetrahydrocannabinol |
| Product type: | Medicine |
| Brand name: | Paracetamol |
| Generic name: | Paracetamol |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Promethazine |
| Generic name: | Promethazine |
| Registration: | Yes - NL intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 01-09-2015 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 04-09-2015 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2015-003496-30-NL |
| CCMO | NL54643.056.15 |